

Acute Coronary Syndromes

PHARMACODYNAMICS OF VORAPAXAR, A PLATELET PAR-1 ANTAGONIST, AND ITS INTERACTION WITH P2Y12 RECEPTOR PATHWAY IN THE TRA-CER TRIAL

ACC Oral Contributions
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Background: The TRACER trial compared vorapaxar, a novel oral PAR-1 antagonist, with placebo, as add-on therapy to standard of care, among 12944 NSTEMI ACS patients who were predominantly treated with aspirin and clopidogrel. While vorapaxar was associated with a significant increase in major bleeding in the overall population, a lower bleeding hazard was observed in those without concomitant clopidogrel.

Methods: A substudy evaluated biologic parameters including platelet reactivity in the placebo and vorapaxar arms (n=249). Platelet aggregation (PA) in response to 20 μ M ADP, 15 μ M TRAP, and CAT (2.5 μ g/ml collagen related peptide + 5 μ M ADP + 15 μ M TRAP)), and P2Y12 signaling using the VASP assay were measured. Results were evaluated at baseline and at 1 mo. Onset of PAR-1 inhibition was evaluated by TRAP PA at 30 min, 1, 2, and 4 hr post loading dose.

Results: At 1 mo TRAP PA was strongly inhibited by vorapaxar with all subjects having < 20% PA within 2-4 hr. ADP maximal and final (5 min post agonist) PA trended lower in the vorapaxar group vs placebo whereas CAT maximal and final PA were significantly lower in the vorapaxar arm. VASP Platelet Reactivity Index (PRI) was significantly lower in both treatment arms.

Conclusions: Vorapaxar had a consistently marked PA inhibition to the PAR-1 agonist TRAP. PAR-1 antagonism may downregulate P2Y12 dependent pathways affecting aggregate stability. Findings imply that concomitant PAR-1 and P2Y12 blockade in the background of aspirin may contribute to an increased bleeding risk.

Maximal Aggregation (MA)		
	Placebo	Vorapaxar
TRAP (15 μ M)	n=33	n=33
Baseline	64 \pm 15	60 \pm 16
1 Month	63 \pm 18	4 \pm 4
p	0.650	< 0.001
ADP (20 μ M)	n=35	n=33
Baseline	56 \pm 17	55 \pm 15
1 Month	52 \pm 22	48 \pm 16
p	0.370	0.090
CAT	n=34	n=31
Baseline	75 \pm 10	74 \pm 14
1 Month	72 \pm 15	44 \pm 18
p	0.159	0.001
Final Aggregation (FA)		
ADP (20 μ M)	n=35	n=31
Baseline	45 \pm 22	43 \pm 19
1 Month	41 \pm 27	34 \pm 20
p	0.433	0.085
CAT	n=34	n=31
Baseline	69 \pm 14	67 \pm 17
1 Month	63 \pm 19	30 \pm 22
p	0.067	< 0.001
VASP PRI (Baseline >75)		
	n=37	n=30
Baseline	83 \pm 5	83 \pm 4
1 Month	64 \pm 24	57 \pm 22
p	< 0.001	< 0.001